November 14, 2002

Dr. Susan Anderson Lewis
Technical Contact
The American Chemistry Council's Phosphoric
Acid Derivatives Panel
1300 Wilson Boulevard
Arlington, VA 22209

Dear Dr. Lewis:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Phosphoric Acid Derivatives Category posted on the ChemRTK HPV Challenge Program Web site on January 15, 2002. I commend The American Chemistry Council's Phosphoric Acid Derivatives Panel for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that The American Chemistry Council's Phosphoric Acid Derivatives Panel advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
A. Abramson
W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Phosphoric Acid Derivatives Category

SUMMARY OF EPA COMMENTS

The sponsor, the Phosphoric Acid Derivatives Panel of the American Chemistry Council, submitted a test plan and robust summaries to EPA for the "Phosphoric Acid Derivatives" category, dated December 13, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on January 15, 2002. The category consists of two sponsored chemicals, tris(2-ethylhexyl) phosphate (CAS no. 78-42-2) and 2-ethylhexyl phosphate (CAS no. 12645-31-7). Three nonsponsored chemicals were included for supporting data: dibutyl hydrogen phosphate (CAS no. 107-66-4), tributyl phosphate (CAS no. 126-73-8), and bis(2-ethylhexyl) hydrogen phosphate (CAS no. 298-07-7).

EPA has reviewed this submission and has reached the following conclusions:

1. Category Definition. The submitter has adequately defined the category of mono-, di-, and tri-esters, except clarity is needed to differentiate between CAS No. 12645-31-7 (sponsored compound that may be a mixture) and CAS No. 1070-03-7 (apparently the pure 2-ethylhexyl phosphate that has not been included in this category).

2. Category Justification. EPA questions the inclusion of the monoester (CAS No. 12645-31-7) in this category for health effects and ecological endpoints. The metabolism data presented by the submitter indicate conversion of the tri-ester to the di-ester but not to the monoester. In addition, the BUA (1992) report referenced to support the proposed category indicates that alkyl phosphoric acid esters can be grouped by di- and tri- esters with no mention of monoesters. Finally, the BUA report treats butyl esters separately from 2-ethylhexyl esters. Thus, the most appropriate approach appears to be treating the mono- (CAS No. 12645-31-7) and tri- (CAS No. 78-42-2) esters as separate chemicals, with the possible use of the di-ester (CAS No. 298-07-7) as an analogue for the tri-ester.

3. Physicochemical Properties and Environmental Fate. The submitter needs to provide measured melting point and water solubility data for the monoester (CAS No. 12645-31-7), and measured hydrolysis data for both the mono- and tri-ester (CAS No. 78-42-2).

4. Health Effects. EPA considers the mono- (CAS No. 12645-31-7) and tri-(CAS No. 298-07-7) esters as independent chemicals which do not belong in the proposed category, and therefore none of the health endpoints have been met for the monoester. In addition, testing is necessary for the reproductive/developmental toxicity endpoint for the tri-ester because the closest analog (CAS No. 298-07-7) also has a data gap for this endpoint. Finally, the robust summaries for the genotoxicity studies with the tri-ester (CAS No. 298–07-7) needs more details to determine whether this endpoint has been met.

5. Ecological Effects. EPA disagrees with the submitter's proposal for no additional ectoxicity testing. Acute fish and invertebrate testing is needed for the monoester (CAS no. 12645-31-7). EPA reserves judgment on the adequacy of the monoester algal study pending submission of missing critical data elements. No further testing is recommended for the tri-ester (CAS no. 78-42-

2) because it has an estimated log K_{ow} of > 8 and low water solubility.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA COMMENTS ON THE PHOSPHORIC ACID DERIVATIVES CATEGORY SUBMISSION

Category Definition

The submitter proposed a category of two sponsored chemicals, 2-ethylhexyl phosphate (CAS No. 12645-31-7) and tris(2-ethylhexyl) phosphate (CAS No. 78-42-2) and added dibutyl hydrogen phosphate (CAS No. 107-66-4), tributyl phosphate (CAS No. 126-73-8) and bis(2-ethylhexyl) phosphate (CAS No. 298-07-7) to provide supporting data.

The submitter needs to clarify the identity of '2-ethylhexyl phosphate' (CAS No. 12645-31-7). The test plan (page 4/14) depicts this as a mono ester derivative, although ChemIDplus (http://chem.sis.nlm.nih.gov/chemidplus/) lists 'phosphoric acid, esters with 2-ethylhexanol' as a synonym, indicating a mixture. The molecular formula listed in ChemIDplus also indicates a mixture. ChemIDplus assigns a different registry number to the pure 2-ethylhexyl phosphate [also known as mono(2-ethylhexyl) phosphate]: CAS No. 1070-03-7. If the mixture is the intended category member, then information is needed on the percent composition of the components.

Category Justification

The following assumes that the submitter intends to use the pure monoester in its analysis.

The submitter's justification for the category is the structural similarity between its members and the implication that these chemicals were treated as a category in a German government report (BUA, 1992). The two sponsored compounds and the non-sponsored, bis(2-ethylhexyl) phosphate, purportedly complete a sequence of mono-, bis- and tris(2-ethylhexyl) phosphates. Because there are limited existing data for the bis(2-ethylhexyl) phosphate, the submitter relies extensively on data obtained from dibutyl hydrogen phosphate and tributyl phosphate.

Dibutyl hydrogen phosphate was chosen as an analog for 2-ethylhexyl phosphate, because of their identical molecular weights. This approach ignores the differences in the extent of alkylation of the two compounds, which can have an effect on the metabolism (as noted by the submitter) and the toxicological properties of these compounds and cannot be used to support a comparison between these two molecules. The submitter also uses a metabolism argument to support grouping the phosphate esters together noting that the tri-esters are rapidly hydrolyzed to the di-esters, but that the di-esters are not hydrolyzed readily to the monoesters. This reasoning, however, does not support a read-across approach using data from dibutyl phosphate to infer the behavior of 2-ethylhexyl phosphate because little or no monobutyl phosphate would be present following exposure to the di- or tri-ester.

EPA notes that the BUA report identifies phosphoric acid esters as a large group and divides them into four subgroups: alkyl phosphates, aryl phosphates, thiophosphoric acid esters, and alkyl phosphites. In the alkyl phosphate group are four substances: dibutyl hydrogen phosphate and tributyl phosphate; and bis(2-ethylhexyl) hydrogen phosphate and tris (2-ethyl hexyl) phosphates. The monoester (2-ethylhexyl

phosphate) is not mentioned because the available data on metabolism, as pointed out by the submitter, suggest the tri-ester is metabolized to the di-ester, but only a small amount appears to be further metabolized to the monoester. The report suggests that, for health effects, the 2-ethylhexyl esters be only compared to each other and the same with the butyl esters (see pages 83-84 in BUA, 1992).

Finally, submitted data from fish, invertebrate, and algal studies of the non-sponsored analog chemicals do not appear to establish a pattern of toxicity that is related to the number of alkyl substituents or the total number of carbon atoms per molecule.

Therefore, EPA considers the submitter's category justification for health and ecological effect endpoints inadequate for the purposes of the HPV Challenge Program.

Test Plan

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient)

The test plan for boiling point, vapor pressure and partition coefficient is adequate for the purposes of the HPV Challenge Program.

The submitter needs to add the physicochemical endpoints in Table 5 - Summary of data (page 13) of the test plan.

Melting point. The submitter provided only an estimated melting point for 2-ethylhexyl phosphate. The submitter needs to provide a measured melting point value for this chemical (following OECD guidelines). Furthermore, the submitter needs to indicate whether the values obtained from safety data sheets are measured or calculated.

Water solubility. The submitter states that the water solubility of 2-ethylhexyl phosphate may be less than 40 mg/L, and that "the product does not appear to be soluble". However, according to OECD guideline 105, quantitative values are required unless a value is expected to be #1 µg/L. The water solubility for this test compound needs to be measured according to OECD guidelines.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The test plan for photodegradation, biodegradation, and transport and distribution is adequate for the purposes of the HPV Challenge Program.

Stability in water. It is stated in the test plan in Table 5 on page 13 that the requirement for this endpoint has been fulfilled and that no additional testing is necessary. This conclusion is based upon an attempt by the submitter to conduct hydrolysis testing according to OECD guidelines for 2-ethylhexyl phosphate and on data submitted for a structurally-similar compound, tributyl phosphate. The submitter states that obtaining an aqueous solution of 2-ethylhexyl phosphate for testing at 400 and 40 mg/L was not possible. Tributylphosphate was not readily hydrolyzed at environmentally relevant pH values. However, EPA notes that phosphoric acid esters are expected to hydrolyze, particularly at alkaline pH values. Therefore, the submitter needs to perform hydrolysis testing on both the mono and tri- 2-ethylhexyl ester compounds. EPA suggests using a lower initial concentration of 2-ethylhexyl phosphate.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, reproductive and developmental toxicity)

The submitter is proposing that no additional testing is required. EPA disagrees that the mono and tri-2-ethylhexyl phosphate esters form a category, but should be considered as individual chemicals. Therefore, none of the health endpoints have been met for the monoester. In addition, the available data for the di- and tri- butyl esters are not appropriate to extrapolate to the monoester for reasons specified below.

There are no health effects data for the mono-2-ethylhexyl ester, and the submitter proposes that a read across strategy be used. The only health effects data submitted were for tri- (sponsored) and bdi- (non-sponsored) 2-ethylhexyl esters and for tri- and di- (both non-sponsored) butyl esters. The submitter notes that the derivatives demonstrate decreasing toxicity with increasing molecular weight, but ignores the degree of substitution. For both acute and repeated-dose toxicity, the test plan predicts that the toxicity of the mono-2-ethyhexyl ester will be similar to that "of dibutyl hydrogen phosphate (107-66-4) of the same molecular weight" (page 7/14). Thus, the submitter ignores the implications of mono- versus di- or tri-substitution on chemical reactivity and metabolism. This is done even though the submitter indicates that the degree of substitution is important in the metabolism of this class of compounds. In addition, the dibutyl hydrogen phosphate repeated-dose study used a test substance that contained only 62.6% diester; the remainder was 18.3% mono-ester and 19.1% triester and "other" (p. 12 of IUCLID file).

EPA notes that according to the TSCATS database, studies for 2-ethylhexyl phosphate as CAS No. 1070-03-7 are available for acute toxicity and genotoxicity (http://esc.syrres.com/efdb/TSCATS.htm).

EPA agrees with the submitter that data are available for tris (2-ethylhexyl) phosphate for all the health endpoints except developmental/reproductive toxicity. This is a data gap for both the tris (2-ethylhexyl) phosphate and the nearest analog [bis(2-ethylhexyl) phosphate]. In addition, the genotoxicity robust summaries need more details to better determine whether this endpoint has been met.

Ecotoxicity

2-Ethylhexyl phosphate. EPA disagrees with the submitter's proposal of no additional ectoxicity testing. Additional testing is needed for fish and invertebrates. The submitter used the ECOSAR program to estimate aquatic toxicity for this chemical, however, such a prediction is not appropriate for this chemical class in ECOSAR. EPA reserves judgment on the adequacy of the algae study with 2-ethylhexyl phosphate pending the submission of missing critical data elements. Finally, EPA notes that according to the TSCATS database, studies for 2-ethylhexyl phosphate as CAS No. 1070-03-7 are available for aquatic toxicity in fish (http://esc.syrres.com/efdb/TSCATS.htm).

tris (2-Ethylhexyl) phosphate. Although there were many inadequacies in the study summaries, EPA suggests that an analysis based on this chemical's physicochemical properties, including extremely low water solubility, support the submitter's conclusion that no further testing is necessary. No ecotoxicity testing is recommended because its high estimated log K_{ow} (>8) and low water solubility suggest a lack of acute or chronic toxicity.

Specific Comments on the Robust Summaries

EPA is not commenting on the dibutyl hydrogen phosphate and tributyl phosphate robust summaries because it believes they do not contribute to the evaluation of the submission.

Chemistry

For those melting point, boiling point and vapor pressure values obtained from MSDS sheets, the submitter needs to indicate whether the data are measured or calculated, and if measured, the method used.

Health Effects

Most robust summaries did not meet EPA guidance for completeness.

Tris (2-ethylhexyl) phosphate*:*

Repeated- Dose Toxicity. The robust summary for a 13-week assay in rats exposed by gavage 5 days/week needs to include the group size and the size of body weight effects.

Genetic Toxicity. Robust summaries for five negative genotoxicity assays (three for mutation in *Salmonella typhimurium*, one for chromosomal aberration and one for sister chromatid exchange assay in Chinese hamster ovary cells) did not provide sufficient information to evaluate the studies. The robust summaries need to include the purity of the test material, the number of replicates/cells examined, the source of the metabolic activation system, positive controls, and the tested and cytotoxic concentrations. No information was provided on the compliance of the studies with GLP/OECD guidelines.

Ecotoxicity Studies

Algae. 2-Ethylhexyl phosphate. Missing study details included the following: test substance (whether salt or neutralized form was used), test purity, test substance concentrations, number of replicates per concentration, test conditions (temperature, pH, and lighting), use of proper controls, signs of toxicity per concentration, control response, study citation, GLP compliance, study guideline, and statistical methods.

Follow-up Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.